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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
08/970,636	11/25/97	RABBANI E	LNZ-53DIV3

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ART UNIT	PAPER NUMBER
1635	9

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Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

1- File Copy

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*U.S. GPO 1996-404-496/40510

Office Action Summary

Application No.	Applicant(s)
08/978,636	Rabbani et al.
Examiner	**Group Art Unit**
Schmidt	1635

—The MAILING DATE of this communication appears on the cover sheet beneath the correspondence address—

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, such period shall, by default, expire SIX (6) MONTHS from the mailing date of this communication .
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).

Status

☐ Responsive to communication(s) filed on _____.

☐ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 1 1; 453 O.G. 213.

Disposition of Claims

☑ Claim(s) 2-24 and 245-260 is/are pending in the application.

Of the above claim(s) _____ is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☑ Claim(s) 2-24 and 245-260 is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claim(s) _____ are subject to restriction or election requirement.

Application Papers

☑ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119 (a)-(d)

Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 11 9(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 1 7.2(a)).

*Certified copies not received: _____.

Attachment(s)

☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

☑ Notice of Reference(s) Cited, PTO-892

☑ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Interview Summary, PTO-413

☐ Notice of Informal Patent Application, PTO-152

☐ Other _____

Office Action Summary

Part of Paper No. 9

DETAILED ACTION

1. This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825 for the reason(s) set forth on the attached Notice To Comply With Requirements For Patent Applications Containing Nucleotide Sequence And/Or Amino Acid Sequence Disclosures: Sequences in this specification and/or the claims are not referenced by sequence identifiers.

Double Patenting

2. A rejection based on double patenting of the "same invention" type finds its support in the language of 35 U.S.C. 101 which states that "whoever invents or discovers any new and useful process ... may obtain a patent therefor ..." (Emphasis added). Thus, the term "same invention," in this context, means an invention drawn to identical subject matter. See *Miller v. Eagle Mfg. Co.*, 151 U.S. 186 (1894); *In re Ockert*, 245 F.2d 467, 114 USPQ 330 (CCPA 1957); and *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970).

A statutory type (35 U.S.C. 101) double patenting rejection can be overcome by canceling or amending the conflicting claims so they are no longer coextensive in scope. The filing of a terminal disclaimer cannot overcome a double patenting rejection based upon 35 U.S.C. 101.

3. Claims 2-24 are provisionally rejected under 35 U.S.C. 101 as claiming the same invention as that of claims 2-24 of copending Application Nos.: 08/978,632, 08/978,633, 08/978,634,

08/978,635, 08/978,637, 08/978,638, 08/978,639, and 08/574,443. This is a provisional double patenting rejection since the conflicting claims have not in fact been patented.

4. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321© may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

5. Claims 255, 257, 259 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 245-247 of copending Application No. 08/978,635. Although the conflicting claims are not identical, they are not patentably distinct from each other because the instant claims are drawn to the nucleic acid construct "which when introduced into a cell produces a nucleic acid product..." and claims 245-247 of '635 are drawn to "a process for... expressing a nucleic acid product in a cell...." The claimed construct is obvious from the method claimed.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claim Rejections - 35 USC § 112

6. Claims 2-21 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 2-21 are indefinite because they depend from canceled claim 1. Therefore, claims 2-21 do not depend on any independent claim.

7. Claims 2-21 and 245-260 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The constructs taught in the claims 2-24 are broadly drawn to a multitude of possible nucleic acid based constructs for use in a cell to produce a product (and in any context, *in vivo* or *in vitro*), comprising: (1) the construct as linear or circular, (2) the construct as comprising 1,2 or 3 strands, (3) comprising a terminus, a polynucleotide tail which can hybridize, (4) composed of RNA or DNA or combinations, (5)containing chemically modified nucleotides or analogs, (6) containing non-nucleic acid entities composed of polymers or ligands or a combination, (7) further specifying the natural and synthetic polymers, the synthetic homo- or heteropolymer with a net

charge, (8)the construct imparting a "further biological activity" by the modified nucleotide, analog, entity, ligand or combination of those, further defined as nuclease resistance, cell recognition, cell binding, and cellular or nuclear localization or a combination, (9) a ligand attached to one of the modified nucleotides, etc. of claim 1, further described as attached to a "segment" or "tail" of the construct , and further defined as being a macromolecule or small molecule or combination. Claims 22-24 describe a second construct "which when present in a cell produces a product, said construct being bound non-ionically to an entity comprising a chemical modification or a ligand."

Claims 245-254 are drawn to another broad genus of nucleic acid constructs for co-expression of a non-native polymerase and another nucleic acid sequence from the construct in a cell, again in any context, *in vivo* or *in vitro*. Dependent claims include the limitations: (1) a recognition site for the polymerase, (2) where the recognition site is complementary to a primer for the polymerase, (3) where the primer is tRNA, (4) where the polymerase is DNA polymerase, RNA polymerase, reverse transcriptase, or a combination, (5) where the RNA polymerase is a bacteriophage RNA polymerasc, either T3, T7, SP6 or a combination, (6) a promoter for the RNA polymerase, (7) the nucleic acid produced is DNA, RNA, or a hybrid, chimera, or a combination and is sense or antisense DNA or RNA.

Claims 255-260 are drawn to another broadly claimed nucleic acid based construct for producing a non-native processing element product in a cell which is substantially removed during

processing (again, the claims could be read in any context, *in vivo* or *in vitro)*. The limitations further include: (1)an RNA processing element, selected from an intron, a polyadenylation and a capping element, or a combination, (2) a single stranded nucleic acid product, (3) a nucleic acid product selected from antisense RNA, antisense DNA, sense RNA, sense DNA, a ribozyme and a protein binding nucleic acid sequence or a combination, (4) and wherein said protein binding nucleic acid sequence comprises a decoy that binds a protein required for viral assembly or replication.

The specification teaches several constructs designed for entry into a cell and expression of one or more sequences to perform a biological function such as antisense inhibition of a nucleic acid. Specifically, several CHENAC constructs are taught prophetically, and pictured in figures 1-13 as vector based constructs constructed by using modified nucleic acid regions and designed to provide improved entry into a cell by way of improved construct-cell interaction. A second group of nucleic acid fused with antibody based constructs are taught prophetically and shown in figures 14-21. Preparation of multimeric insulin by means of nucleic acid hybridization is further taught prophetically and shown in figures 22-23. No exemplification for such constructs is taught in the specification as filed.

Furthermore, vectors ultimately designed for antisense inhibition of HIV in cells by co-expression of antisense DNA under control of a T7 promoter with a T7 polymerase (represented in figures 24-49) are taught and supported by *in vitro* data. Specifically, construction of the M13

phage vectors pRT-A, pRT-B, and pRT-c are taught which contain the coding sequence for the T7 RNA polymerase driven by the RSV promoter and with an SV40 intron sequence that will be spliced out to form a functional polymerase enzyme and each respective construct also having the antisense A, B, and C sequences driven by a T7 promoter and terminated by a T7 terminator. A modified version of the pINT-3 construct (the parent vector of pRT-A, B and C vectors before insertion of the antisense sequences) is taught where a polylinker is inserted behind the poly-A tail of the T7 polymerase gene for subsequent sub-cloning of the lacZ gene in this instance to form pINT-LacZ. The result upon introduction in a eukaryotic cell would be synthesis of the T7 polymerase from the RSV promoter which in turn acts upon the T7 promoter to synthesize B-galactosidase.

Furthermore, plasmids are taught containing anti-sense segments introduced into the transcript region of the U1 gene, plasmid pHSD-4 U1 so that upon expression of the transcript, the antisense RNA sequence is produced to the complementary region of the HIV genome. Specifically, pDU1-A, B, C and D were made using the antisense A, B, and C sequences previously described and D as a control containing a non-HIV sequence. A multi-cassette version of the constructs was also made by sub-cloning in tandem the A,B, and C antisense to make pNDU1 (A,B,C) (N meaning the construct was also contained the gene for neomycin resistance).

Other multi-cassette constructs taught were:

(1) TRI 101, an M13 phage vector containing the "A" antisense T7 operon , the "B" antisense T7 operon and the "C" antisense T7 operon in a single construct (figure 46). Co-transfection would be required for expression of the antisense molecules from this construct with a vector that expresses T7 RNA polymerase (suggested is the intron containing construct of example 19); and,

(2) an M13 construct constructed from a multi-ligation of portions of pINT-3 (containing the intron containing polymerase) and the T7 promoter driven A, B, and C sequences (see figure 47).

The specification teaches application of some of these constructs ("various U1 constructs described above" p. 167, last line) in antisense inhibition of HIV in infected U937 cell culture. Specifically the following is shown: (1) expression of A, B, and C antisense by hybridization analysis after expression of the "U1 clone" (p. 169, line 3), (2) expression of the "triple U1 construct" (p. 169, para. (c), line 1) which result in a decrease in p24 production next to the control. and increased % reduction in p24 over time and after re-infection of cells, and these results were confirmed by absence p24 amplification next to control cells via PCR of the targeted DNA, and (3) expression of the construct of figure 50, a fusion product antisense A upstream of B-gal gene where antisense activity of the A portion caused inhibition of B-gal activity as shown in lacZ assays. The results in figure 51 show HIV A/Anti-A activity and HIV A/Anti-ABC (when the triple U1 construct was used by *co-transfection*) as the equivalent of the uninfected cells

whereas the infected and control containing cells showed high B-gal expression. Therefore, it does not appear in the specification as filed that the multicassette A,B,C and T7 polymerase construct (expressed on same plasmid) was applied to the same HIV challenge experiments.

Additional constructs are more prophetically taught: the primary nucleic acid construct that propagates production centers for the production of single-stranded antisense, etc. in examples 21-25, and the retrovirus vector containing sequences for the expression of antisense RNA directed at HIV on page 181, last para.

Claims 22-24 read on any construct bound non-ionically to a ligand or otherwise chemically modified entity, further limited as having a polynucleotide tail terminus and where the tail is hybridized to a complementary polynucleotide sequence. The breadth of genus sought for such is not enabled in view of the lack of specificity of guidance in the specification as filed. The specification fails to provide guidance for the breadth claimed since the claims vaguely claim "constructs" which "produce products." The specification teaches only by way of example HIV inhibition by antisense expression from vector constructs which do not entail chemical modified entities nor polynucleotide termini.

Claims 255-260 are further broadly drawn to a nucleic acid construct for producing a product in a cell which includes a "processing element" that is "substantially removed during processing" in a "compatible cell." The language "processing element" reads on expression of any gene from said construct that has a "processing" function in a cell, for example, any ribozyme,

polymerase, or any protein causing a modification of any molecule (protein or DNA)in a cell. The scope of the genus sought for such constructs is not enabled in view of the lack of specificity of guidance in the specification as filed. The specification fails to provide guidance for the breadth claimed since the claims nebulously claim "constructs" which produce "products" having a "processing" function. The specification teaches only prophetically an intron containing polymerase wherein the intron is removed in a compatible cell. The specification does not exemplify application of the T7 polymerase/U1-A,B,C vector as described in example 19 in cells. It appears that only the U1A,B,C clone co-expressed with T7 polymerase (on another vector) is exemplified in the HIV challenge and LacZ assays.

Furthermore, the claims specify the context for producing the product in a cell and no exemplification of whole organism success is found in the specification as filed. There is a high level of unpredictability in the antisense art and analogous gene therapy art for *in vivo* (whole organism) applications. The factors considered barriers to successful delivery of antisense delivery to the organism are: (1) penetration of the plasma membrane of the target cells to reach the target site in the cytoplasm or nucleus, (2) withstanding enzymatic degradation, and (3) the ability to find and bind the target site and simultaneously avoid non-specific binding (see Branch). Despite the synthesis of more resilient, nuclease resistant, oligonucleotide backbones and isolated successes with antisense therapy *in vivo*, the majority of designed antisense molecules still face the challenge of successful entry and localization to the intended target and further such that antisense

and other effects can routinely be obtained. Note Flanagan et al. who teach "although numerous reports have cited antisense effects using oligonucleotides added to cell medium, direct proof that oligonucleotides enter cells and affect gene inhibition by an antisense mechanism is still lacking (page48, column 1)."

Specifically, *in vitro* results with one antisense molecule are not predictive of *in vivo* (whole organism) success. *In vitro*, antisense specificity to its target may be manipulated by "raising the temperature or changing the ionic strength, manipulations that are commonly used to reduce background binding in nucleic acid hybridization experiments." (Branch, p. 48) Discovery of antisense molecules with "enhanced specificity" *in vivo* requires further experimentation for which no guidance is taught in the specification. Note Branch who teaches the state of the art for designing an antisense which inhibits a target *in vivo:* it "is very difficult to predict what portions of an RNA molecule will be accessible *in vivo*, effective antisense molecules must be found empirically by screening a large number of candidates for their ability to act inside cells (Branch, p.49)." And in the instant case, the claims read broadly on administration of an antisense inhibitor in any cell, therefore the whole organism included While the specification teaches cell culture inhibition, no evidence of successful *in vivo* (whole organism) antisense inhibition has been shown, nor do the culture examples correlate with whole organism delivery.

One of skill in the art would not accept on its face the successful delivery of the disclosed antisense molecules *in vivo* in view of the lack of guidance in the specification and the

unpredictability in the art. Specifically the specification does not teach (1) stability of the antisense molecule *in vivo*, (2)effective delivery to the whole organism and specificity to the target tissues, (3) dosage and toxicity, nor (4) entry of molecule into cell and effective action therein marked by visualization of the desired treatment effects. These key factors are those found to be highly unpredictable in the art as discussed *supra*. The lack of teaching of these factors in the specification as filed, coupled to the amount of "trial and error" experimentation involved in the deduction of such results would lead one skilled in the art to necessarily practice an undue amount of experimentation for whole organism use of the claimed constructs.

No determination of enablement can be made for claims 2-21 because there is no independent claim from which they depend. Without knowing what claims 2-21 depend on, the full scope of the claims is not known.

8. Claims 2-24 and 245-260 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 2-21 are drawn to a missing independent claim and therefore the scope claimed is not able to be determined. Claims 22-24 are drawn to a broad scope of constructs which are bound non-ionically to an entity having a chemical modification or a ligand and produce a product

in a cell. Claims 255-260 are further broadly drawn to a nucleic acid construct for producing a product in a cell which includes a "processing element" that is "substantially removed during processing" in a "compatible cell."

The claims broadly encompass "constructs" for producing a "product" and it is not clear what is embraced by the claims. The claims read on vectors, genomes, cell processes like translation, transcription, etc. Furthermore, the scope of "chemical modification" as used in claim 22 is not clear in relation to the construct.

The instant specification describes prophetically a number of potential modified nucleic acid constructs for expression of an entity in a cell. The supporting figures provide limited additional disclosure of relevant identifying structural characteristics because they primarily correspond to expression vector based constructs which are only one facet of the invention in light of the nebulous scope claimed.

Clearly the specification only considers vector-like constructs for delivery and expression of nucleic acids. Specifically, for claims 255-260, use of processing elements other than the SV40 intron are not taught in a whole construct for subsequent functional use of production of nucleic acid products in claim 259 or protein binding nucleic acid sequences of claim 260.

Furthermore, the actual constructs used in the HIV challenge and Lac-Z assays taught in the specification are not described in clear and exact terms (p. 169, line 3 recites "U1 clone"; p. 169, para. © line 1 recites "triple U1 construct"; and p. 167, last line recites "various U1

constructs described above') and it is not clear whether the constructs used had the intron sequence in the T7 polymerase, or even which constructs were used in the assays.

Despite the known predictability of standard vector construction in the molecular biology art, in view of the nearly infinite scope claimed and the lack of adequate description in the specification for such a broad genus of possible "constructs," coupled with the high level of unpredictability for constructs which could fall within this genus such as those involving gene therapy, the specification as filed fails to provide one skilled in the art enough description to show possession of a representative number of "construct" species for the breadth claimed.

See the June 15, 1998 (Vol. 63, No. 114, Pages 32639-32645) Federal Register for the interim guidelines for the examination of patent applications under the 35 U.S.C. 112 "Written Description" requirement.

Claim Rejections - 35 USC § 102

9 The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

10. Claims 245-249, and 253 are rejected under 35 U.S.C. 102(e) as being anticipated by Saito et al.

The claimed invention is drawn to a nucleic acid construct for co-expression of a non-native polymerase causing expression of another nucleic acid sequence in a cell. Further limitations include use of a tRNA primer and reverse transcriptase.

Saito et al. teach a vector for expression of retroviral genes in a cell, including expression of reverse transcriptase for production of genes associated with the action of the reverse transcriptase from a tRNA primer.

11. Claims 245-247, and 249-254 are rejected under 35 U.S.C. 102(e) as being anticipated by Wagner et al.

The claimed invention is drawn to a nucleic acid construct for co-expression of a non-native polymerase causing expression of another nucleic acid sequence in a cell. Further limitations include use of a bacteriophage polymerase such as T3, T7 or SP6 and antisense DNA or RNA as the co-expressed nucleic acid sequence.

Wagner et al. teach a vector construct for co-expression of an RNA polymerase (ex. T3, T7 or SP6, see col.8 line 11) with a gene of interest (for example, antisense, ribozyme or any other gene the scope of which would include a nucleic acid sequence coding for a decoy to a viral

protein) for enhancement of gene expression in cells. It is further within the scope of the invention to select a gene encoding an intron or a capping element for a polyadenylation signal.

12. Claims 22-24 are rejected under 35 U.S.C. 102(e) as being anticipated by Meyer et al..

The claimed invention is drawn to any construct which when present in a cell produces a product, and is bound non-ionically to an entity comprising a modification or a ligand, and further comprises a hybridized polynucleotide tail.

Meyer et al. teach a covalently linked conjugate of an oligonucleotide (ODN) with a peptide and a carrier or targeting ligand (ODN-peptide-carrier) including a therapeutic oligonucleotide which is capable of selectively binding to a target sequence of DNA, RNA or protein inside a target cell. The invention of Meyer et al. Reads on all of the instant claimed limitations for a non-naturally occurring construct for production of a product in a cell (in Meyer, an antisense oligonucleotide is produced).

13. Claims 255-260 are rejected under 35 U.S.C. 102(e) as being anticipated by Sullenger et al..

The claimed invention is drawn to a nucleic acid construct which when introduced into a cell produces a nucleic acid product comprising a non-native processing element, which when in a compatible cell, said processing element is substantially removed during processing. Further

limitations include an RNA processing element (an intron or a polyadenylation signal and capping element), and the nucleic acid product being: single stranded, antisense DNA or RNA, sense DNA or RNA, a ribozyme or a protein binding sequence such as one that binds protein required for viral assembly or replication.

Sullenger et al. teach expression of RNA-based inhibitors of viral replication by localization of an inhibitory RNA such as a ribozyme to the target. Ribozymes are known in the art to have a processing function and also have an inherent half-life and are therefore removed.

14. Claims 255-260 are rejected under 35 U.S.C. 102(e) as being anticipated by Hurwitz et al..

The claimed invention is drawn to a nucleic acid construct which when introduced into a cell produces a nucleic acid product comprising a non-native processing element, which when in a compatible cell, said processing element is substantially removed during processing. Further limitations include an RNA processing element (an intron or a polyadenylation signal and capping element), and the nucleic acid product being: single stranded, antisense DNA or RNA, sense DNA or RNA, a ribozyme or a protein binding sequence such as one that binds protein required for viral assembly or replication.

Hurwitz et al. teach selective use of introns in an expressed gene for increased expression of the gene in a mammalian cell, specifically the product is human serum albumin.

15. Claims 255-260 are rejected under 35 U.S.C. 102(b) as being anticipated by DeYoung et al..

The claimed invention is drawn to a nucleic acid construct which when introduced into a cell produces a nucleic acid product comprising a non-native processing element, which when in a compatible cell, said processing element is substantially removed during processing. Further limitations include an RNA processing element (an intron or a polyadenylation signal and capping element), and the nucleic acid product being: single stranded, antisense DNA or RNA, sense DNA or RNA, a ribozyme or a protein binding sequence such as one that binds protein required for viral assembly or replication.

DeYoung et al. teach expression of ribozymes imbedded in a U1 sequence and under the control of a T7 promoter. Ribozymes are known in the art to have a processing function and also have an inherent half-life and are therefore removed.

Claim Rejections - 35 USC § 103

16. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

17. Claims 245-260 are rejected under 35 U.S.C. 103(a) as being unpatentable over DeYoung et al. as applied to claims 255-260 above in view of Karn et al., Wagner et al., Curiel et al., and Zaia et al..

A. Claims 245-254 are drawn to a nucleic acid construct for co-expression of a non-native polymerase causing expression of another nucleic acid sequence in a cell. Further limitations include use of a bacteriophage polymerase such as T3, T7 or SP6 and antisense DNA or RNA as the co-expressed nucleic acid sequence. Claims 255-260 are drawn to a nucleic acid construct which when introduced into a cell produces a nucleic acid product comprising a non-native processing element, which when in a compatible cell, said processing element is substantially removed during processing. Further limitations include an RNA processing element (an intron or a polyadenylation signal and capping element), and the nucleic acid product being: single stranded, antisense DNA or RNA, sense DNA or RNA, a ribozyme or a protein binding sequence such as one that binds protein required for viral assembly or replication.

B DeYoung et al. teach expression of ribozymes imbedded in a U1 sequence and under the control of a T7 promoter. DeYoung does not teach a cassette style expression of more than one sequence from the same vector, expression of specifically antisense to HIV tat/rev genes, nor co-expression of the T7 polymerase from the same vector.

C. Wagner et al. teach a vector construct for co-expression of an RNA polymerase (ex. T3, T7 or SP6, see col.8 line 11) with a gene of interest (for example, antisense, ribozyme or any

other gene the scope of which would include a nucleic acid sequence coding for a decoy to a viral protein, see column 3) for enhancement of gene expression in cells. It is further within the scope of the invention to select a gene encoding an intron or a capping element for a polyadenylation signal. Wagner does not teach antisense expression to HIV in his claimed construct.

D. Karn et al. teach antisense inhibition of the HIV TAT protein but does not teach co-expression of the antisense RNA with a T7 polymerase.

E. Curiel et al. teach expression of tandem expression of "genetic units"(such as ribozyme or antisense sequences) "when it is simultaneously desired to produce inhibiting RNAs directed against various types of RNA." (See columns 27 and 28) Curiel also teaches the idea of the size of the tandem "genetic units" as a limiting factor in the vector design.

F. Zaia et al. teach ribozymes as representing a "second generation" of antisense molecules for targeting HIV and teach the use of both synthetic antisense DNA and expressed antisense RNA for inhibition of HIV-1. (See page 101)

It would have been prima facie obvious at the time the invention was made for one of ordinary skill in the art to express in tandem antisense directed to HIV sequences from a phage vector containing U1 sequences flanking the antisense molecule (for fused expression and direction to the nucleus) under the control of a T7 promoter and subsequently to co-express the T7 polymerase on the same vector construct.

One of ordinary skill in the art would have been motivated to apply antisense to HIV targets as demonstrated by Karn et al., one example from the art of antisense inhibition of HIV as a method of inhibition of viral proliferation. One of ordinary skill in the art would have been motivated to express the antisense sequences within U1 from a T7 promoter in the context taught by DeYoung for improved targeting of the antisense sequence to the nucleus. Although DeYoung teaches ribozyme placement in the U1 construct, it would have been obvious to exchange antisense nucleic acid sequences for ribozyme sequences, as Zaia teaches ribozymes are functional equivalents of expressed RNA antisense molecules. See further Wagner et al. who also taught expression of ribozymes or antisense equivalently from the same construct (column 3 and 7). One of ordinary skill in the art would have been motivated to express the antisense sequences on the same plasmid as T7 polymerase as taught by Wagner et al. to avoid co-transfection of the polymerase on a second vector for expression of the T7 promoter driven antisense in the mammallian cell. Further, one of ordinary skill in the art would have been motivated to express in tandem from said vector more than one U1-antisense sequence as taught by Curiel et al. for simultaneous application of antisense molecules to different targets.

One of ordinary skill in the art would have had a reasonable expectation of success to express an antisense sequence in place of the ribozyme sequence within a U1 sequence as in the construct taught by DeYoung et al. since Zaia et al. taught ribozymes and antisense were functional equivalents in the art. Wagner et al. further taught the interchangeability of ribozyme

and antisense sequences for expression from a site on a vector (see column 7). One of ordinary skill in the art would have had a reasonable expectation of success to express U1-antisense "genetic units" in tandem (ie, with the associated desired transcriptional units surrounding each antisense sequence) as taught by Curiel with the number of possible units chosen limited only by the size and packaging constraints of the vector. Furthermore, one of ordinary skill in the art would have had a reasonable expectation of success to express a T7 polymerase on the same construct as the U1-antisense sequences as taught by Wagner et al.. Wagner taught the effective expression of the T7 polymerase and application of the expressed polymerase to further express antisense sequences (see column 3 and 7, lines 34-35) under control of a T7 promoter on the same vector construct in a mammallian cell. Therefore, it would have been expected that the U1-antisense to HIV would have been expressed and suffeiciently localized to the target region in the nucleus, and that application of known antisense molecules from the art would have resulted in the effective inhibition of the HIV target in any cell.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to *Mary M. Schmidt*, whose telephone number is (703) 308-4471.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, *George Elliott, Ph.D.* may be reached at (703) 308-4003. The examiner's primary, *John LeGuyader*, may be reached at (703) 308-0447.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

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